Reviewer's report

**Title:** Human genetic selection induced by folate on 677C>T polymorphism of the MTHFR gene

**Version:** 1  **Date:** 23 February 2008

**Reviewer:** Osvaldo Maximo Mutchinick

**Reviewer's report:**

The manuscript “Human genetic selection induced by folate on 677C>T polymorphism of the MTHFR gene”, addresses an interesting aspect respect the possibility that changes in diet, particularly folate fortification of the diet in pregnant women may “protect” embryos and young fetuses against SA.

1. They postulate that this changes induce a selective advantage reflected by an increase of the MTHFR gene TT genotype in the younger population of the region were the study was performed. They support their hypothesis based on the increasing trend of the T allele and TT genotype prevalence during the 20 century to the last quarter of it.

2. The authors also analyze the T allele and TT genotype prevalence in SA considering a shorter period of time grouping their data in 3 years periods staring in 1882 till 1990, comparing their data in SA with controls which are healthy individuals born between 1976 and 2000.

3. That the number of TT SA increased not necessarily need to be associated with an increase with pregnancies that reach term, but with longer duration of pregnancy. In cases of women not receiving periconceptional folate fortification could abort earlier

**Comments:**

Abstract, the author’s expression: “The aim was toâ€¦increase in mutations…” is not exactly what they did. They analyze only one variant and the aim was to analyze a possible increasing trend in the prevalence of the T allele and TT genotype of a particular gene. The conclusion is based only in an historical publication that was impossible to found (Ref: 12). No reference is made to proportion of women in reproductive age that currently have folate fortified diet in Spain. This is a heavy and risky conclusion. Probably or suggest will be a better word to be included, and more precise data on proportion of fortified diets need to be added.

The differences mentioned in Spain and Swiss (ref. 6) were also observed in the Japanese population (Matsushita Sachiyo et al., (1998) that proposed that the decreasing trend with increasing age could be related to death of the TT homozygous due to cardiovascular diseases conditioned by the hyperhomocystenemia the enzymatic defect may produce. In other words, TT
prevalence may be considerable related to age. The analysis of MTHFR genotypes stratifying the sample of SA studied by weeks of gestation will be important to analyze to compare changes in gestation progression related to the selective advantage of the TT genotype in the presence of folate fortification. With respect to folate fortification no concrete information is given and will be important to be included

Authors mentioned that the TT homozygous has been never seen in Africans. That is not true. There are several publications that although found a very low prevalence, between 0.8% to 1.8% (ref: Gueant Rodriguez RM et al., AJCN, 2006; Keku T et al., Cancer Epidemiol Biomarkers & Prevention, 2002, table 2; Wilken B et al, J Med Genet, 2003) the homozygous for the variant in the African population exist.

It is mentioned in the abstract and discussion that in the last quarter of the century that they observed an H-W disequilibrium that I could not confirm. Chi square test of goodness of fit for 1 degree of freedom gives a non significant value (p > 0.35).

Tables need to be improved including the numbers of cases in each category, because to test the finding the authors describe, one need to approximately estimate using percentages.

The publications mentioned above should be included. Others recently published (Altomare I et al, Thrombosis Journal, BioMed Central, 2007, 5:17,) and three interesting meta-analysis cited in this article should be included and discussed.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

'I declare that I have no competing interests'